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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,211	08/22/2006	Jean-Marie Buerstedde	P30753US00	5528

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EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	**PAPER NUMBER**
1633	

NOTIFICATION DATE	DELIVERY MODE
03/23/2012	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

IP.Docketing@aporter.com

Office Action Summary	Application No.	Applicant(s)	
	10/590,211	BUERSTEDDE ET AL.	
	Examiner	Art Unit	
	SUMESH KAUSHAL	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 January 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *29,30,35,44-46,48-59,63,65,67,72 and 74-79* is/are pending in the application.

5a) Of the above claim(s) *30 and 57* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *29 35, 44-46, 48-56, 58-59, 63, 65, 67, 72 and 74-79* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 10/27/10 and 1/31/11 has been acknowledged and fully considered, however is found not fully persuasive in view of new grounds of rejection(s) below. Claims 29, 35, 44-46, 48-56, 58-59, 63, 65, 67, 72 and 74-79 are pending and are examined in this office action. Claims 30 and 57 stand withdrawn in response a restriction election.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29, 35, 44-46, 48-56, 58-59, 63, 65, 67, 72 and 74-79 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for producing a hypermutated transgenic target nucleic acid sequence by transfecting the Chicken DT40 $AID^{R}\psi$ V^{-} B-lymphoid cells with a targeting genetic construct capable of targeting the endogenous V-gene immunoglobulin locus of said cells, does not reasonably provide enablement for any method wherein the hypermutated transgenic target nucleic acid sequence are produced by transfecting a targeting construct in any B-cells (as claimed). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature of Invention

The instant invention relates to a method of producing a hyper-mutated gene of interest in recombinant B-cells.

Breadth of Claims and Guidance Provided by the Inventor

The scope of instant invention encompasses a method of producing hyper-mutated gene of interest in B-cell obtained from chicken, sheep, cow pig or rabbit by transfecting a vector which targets any and all genes found in B-cells.

At very best the specification discloses only one lymphoid cell (Chicken DT40 $AID^{R}\psi$ V^{-} B-lymphoid cells), that contains no mutations in RAD51 or its analogs, and replaces gene conversion by hypermutation (pp. 16-17 of the substitute specification). The specification is silent however on any other genetically modified variants of lymphoid cells from any species of animals, or a DT40 or similar cell that has a hypermutation rate higher than the rate of its non-genetically modified counterpart that contains ψ V donors. Thus it is clear that applicants' description of structure and activity regarding other lymphoid cell variants is based in large part on conjecture. The various genetically modified lymphoid cells having a hypermutation rate higher than the rate of its non-genetically modified counterpart that contains ψ V donors and RAD51 were not known in the prior art at the time of the instant invention by Applicants, and include lymphoid cell variants yet to be discovered. As the specification fails to describe the structure and activity for the genus of variants and genetically modified lymphoid cells, the disclosed single species does not constitute a substantial portion of the claimed genus. The instant specification is devoid of a description for the numerous derivatives and variants of lymphoid cell that retain ψV donors and RAD51 gene activity, but have a hypermutation rate higher than that of a non-genetically modified cell. The specification merely discloses the structure and function of Chicken DT40 $AID^{R}\psi$ V^{-} B-lymphoid cells cell and lymphoid cells having mutations in the RAD51 gene, such as XRCC3, previously described in the prior art, with no other variants or derivatives displaying the requisite biological activity. The skilled artisan would therefore need to engage in further

additional experimentation to discover a lymphoid cell having the desired characteristics of higher hypermutation rates with no deleterious mutations in RAD51 or its analogs. Such experimentation necessarily has unpredictable outcomes and thus constitutes an undue burden on the skilled artisan.

State of Art, Predictability and Quantity of Experimentation Required

The state of the art at the time of filing was such that process of inducing hypermutation in gene of interest is not only complex but is also locus sensitive. Vertebrate B cells are able to diversify their rearranged immunoglobulin (Ig) genes by hypermutation, gene conversion and class switch recombination. All three phenomena require expression of Activation Induced cytidine Deaminase which most likely initiates Ig gene diversification by deaminating cytidines within the mutating and recombining sequences. A further requisite for hypermutation and switch recombination is the transcription of the Ig genes and the switch regions respectively. Sequence analysis of transcribed non-Ig genes from AID expressing B cells revealed either no or only a low number of mutations compared to Ig genes. However, the mutation rates for the non-Ig genes in AID expressing B cells were still orders of magnitude lower than for the Ig genes. To explain this difference between Ig and non-Ig genes it has been postulated that cis-acting sequences in the Ig loci activate hypermutation possibly by recruiting AID. However, intense efforts did not succeed to unambiguously define these sequences for the murine and human Ig loci.

At best the chicken B cell line DT40 diversifies its rearranged Ig light chain (IgL) gene by gene conversion in the presence of nearby pseudo V (ψV) genes and by hypermutation (locus controlled), if the ψV genes are deleted. Both activities strictly depend on the expression of AID. The hypermutation activity of DT40 appeared however to be limited to the IgL locus, because no mutations were found in other highly transcribed non-IgL genes. DT40 has been proposed as a model to study the mechanism of Ig hypermutation because as compared to mice and humans, the chicken IgL locus including the ψV genes is compact spanning only 30 kb. (see. Blagodatski et al, PLoS Genetics 5(1):e100032, 2009, *ref. of record*).

Despite this impressive result, hypermutation is difficult to control in non-chicken B-cells like RAMOS, because transgenes usually integrate at random chromosomal sites outside the hypermutating Ig loci. In contrast, transgenes can be easily inserted into the Ig loci of the chicken B cell line DT40. DT40 diversifies its rearranged Ig light chain gene by pseudo V (ψV) gene-templated gene conversion, but if gene conversion is blocked due to the inactivation of RAD51 paralogues or the deletion of gene conversion donors, hypermutation occurs. Ig gene diversification by conversion or hypermutation requires expression of the AID gene. Based on these results, we reasoned that transgenes inserted into the Ig loci of DT40 without nearby gene conversion donors would be diversified by hypermutation in AID positive cells. (see Arakawa et al, Nucleic Acids Research, 36(1):e1 1-11, 2007, *ref. of record*)

Furthermore ablation of pseudo V (ψV) donors activates AID-dependent Ig hypermutation in DT40 cells. This shows that Ig gene conversion and hypermutation are competing pathways derived from the same AID-initiated intermediate. Furthermore it was proposed that the ψV knockout DT40 as an ideal model system to approach the molecular mechanism of Ig hypermutation and as a new tool for in situ mutagenesis. The results demonstrate that the deletion of the nearby pseudogene donors abolishes Ig gene conversion in DT40 and activates a mutation activity that closely resembles Ig hyper- mutation. The features shared between this new mutation activity and somatic hypermutation include (1) AID dependence, (2) a predominance of single nucleotide substitutions, (3) distribution of the mutations within the 5' transcribed region, (4) a preference for hotspots, and (5) Ig gene specificity. It was concluded that the the AID^R and the ψV knockout DT40 clones are a powerful experimental system to address the role of trans-acting factors and cis-acting regulatory sequences for Ig gene conversion and hypermutation. Compared to alternative animal or cell culture systems, it offers the advantages of (1) parallel analysis of Ig gene conversion and hypermutation, (2) conditional AID expression, (3) easy genome modifications by gene targeting, (4) normal cell proliferation and repair proficiency, and (5) Ig locus specificity of hypermutation. The ability to induce gene-specific hypermutation in the DT40 cell line

might also find applications in biotechnology (see Arakawa et al, PloS Biology 2(7):0967-74, 2004).

At very best the instant specification discloses only one lymphoid cell (Chicken DT40 AID$^{R}\psi$ V^{-} B-lymphoid cells), that contains no mutations in RAD51 or its analogs, and replaces gene conversion by hypermutation (pp. 16-17 of the substitute specification). The specification is silent however on any other genetically modified variants of lymphoid cells from any species of animals, or a DT40 or similar cell that has a hypermutation rate higher than the rate of its non-genetically modified counterpart that contains ψV donors. Furthermore, It is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966), Stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.

In instant case providing producing hypermutated genes via method wherein the hypermutated genes are produced by transfecting any kind of targeting construct in any B-cells (as claimed), thereof is not considered routine in the art and without sufficient guidance to a transgene construct design and specific B-cell type having the required modification; the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore considering the state of the art and limited amount of guidance provided in the instant

specification, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Conclusion

No claims are allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUMESH KAUSHAL whose telephone number is (571)272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sumesh Kaushal/
Primary Examiner, Art Unit 1633

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